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A Comparison of Clonidine with Morphine for Antinociceptive and Antiwithdrawal Actions[1]

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ABSTRACT

Fielding, Stuart, Jeffrey Wilker, Martin Hynes, Mark Szewczak, William J. Novick, Jr. and Harbans Lal: *A comparison of clonidine with morphine for antinociceptive and antiwithdrawal actions.* J. Pharmacol. Exp. Ther. **207:** 899–905, 1978.

Clonidine was found to possess dose-dependent analgesic and antiwithdrawal activity. In mice, clonidine prolonged the tail flick latency and inhibited phenylquinone-induced writhing. In rats, it inhibited tail withdrawal from hot water and a pain response to pressure application on an inflamed paw. The effective doses of clonidine were different in the different tests employed, but they were always smaller than those of morphine. Naloxone failed to antagonize the analgesic actions of clonidine but effectively antagonized those of morphine. Phenoxybenzamine also did not alter the inhibition of tail flick induced by clonidine. Clonidine suppressed morphine withdrawal body shakes in a dose-dependent manner as does morphine. This action of clonidine was not reversed by naloxone. In usual laboratory tests, clonidine appears to be an effective analgesic which antagonizes signs of morphine withdrawal.

Morphine is an effective pain reliever currently available to the physician and it is the standard against which other analgesics are compared. However, the use of narcotics like morphine is hampered by the rapid onset of drug dependence which limits their applications. Current research in analgesics is aimed at a non-narcotic analgesic agent which will alleviate pain without the development of physical dependence and which will be able to block withdrawal symptoms in patients currently receiving narcotic drugs. The antihypertensive agent clonidine was reported to block pain-induced vocalization afterdischarge (Paalzow and Paalzow, 1976) and to reduce certain withdrawal signs in morphine-treated animals (Meyer and Sparber, 1976; Fielding *et al.*, 1977). We have evaluated clonidine for its antinociceptive and anti-withdrawal activity by comparing its effects with those of morphine in the same test systems.

Methods

Male hooded rats of the Long Evans strain weighing 250 to 300 g, female Wistar rats weighing 130 to 175 g and Swiss albino male mice of CD-1 COBS strain weighing 22 to 28 g were used. All drugs were dissolved in saline or suspended in carboxymethylcellulose.

Measurement of analgesia. *Phenylquinone-induced abdominal constriction in mice.* The procedure of Siegmund *et al.* (1957) was modified. Drug was dissolved in distilled water and administered s.c. One-half hour later a 0.125% solution of phenylquinone (phenyl-*p*-benzoquinone, Eastman Organic Chemicals

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[1] A portion of these data was reported at the meeting of the Federation of American Societies for Experimental Biology in 1977 (Fielding *et al.*, 1977).

(Rochester, N.Y.) in 5% ethyl alcohol was injected i.p. into mice at a volume of 10 ml/kg. The injected mice were singly placed in 1-liter glass beakers for observation. Five minutes were allowed for habituation to the beaker after which they were observed for 10 min and the number of abdominal constrictions were recorded for each mouse. An abdominal constriction was defined as occurrence of any one or more of the following postures: 1) an inward rotation of one or more of the feet with twisting and turning of the trunk; 2) drawing in of the abdominal wall; 3) lordosis (arching of the back). The percent inhibition of abdominal constriction was computed by dividing the 100-fold difference between the number of constrictions in drug and control groups by average number of constrictions in control group.

Tail-flick response in mice. Each mouse was held in a mouse holder so that the tail was protruding out on the bench surface. Radiant heat produced by a focused light beam of about 7 V was applied until the mouse flicked his tail. The flick response was recorded through an electronic stopwatch.

Each animal in the test was first screened for reproducibility of response to radiant heat. Two tail flicks were measured at an interval of 15 min. A mouse showing more than 1 sec difference in the flick latency between two measures was discarded. Also, any animal varying more than 3 sec from group mean was discarded. Drugs were dissolved in distilled water and administered s.c. One-half hour after drug administration the animals were again tested and the percent analgesia was determined. Phenoxybenzamine was injected 15 min before clonidine or saline.

Tail-withdrawal in rats. Analgesia in rats was measured by inhibition of tail withdrawal (Janssen *et al.*, 1963) as described recently by Miksic and Lal (1977). Each rat was injected with the drug or vehicle (0.9% saline) and placed in a specially constructed rat holder with his tail protruding out and freely hanging. Thirty minutes after morphine or naloxone administration and 60 min after clonidine administration the distal end of the tail was dipped up to 5 cm in a beaker of water kept at 55°C. The tail withdrawal latency was the time interval at which the tail was withdrawn clearly out of the water. It was recorded through an electronic stopwatch.

Randall-Selitto test in rats. The procedure as described by Randall and Selitto (1957) was modified for this experiment. Female rats were injected s.c. into the plantar region of the left hind paw with 0.1 ml of Brewer's yeast-suspension prepared 20% in distilled water. Three hours after the injection, pressure was applied to both the inflammed paw and to the nontreated paw to measure the threshold pressure which induced a pain response. The pain response was defined as an elicitation of either a struggle, or turning to bite. The pressure was applied through an "analgesia meter" (Ugo Basile Apparatus for Biological Research, Milan, Italy) which permits application of a constantly increasing pressure, measured in grams, until a response is elicited. Before testing, each animal was screened for pain sensitivity. Any animal not responding to a pressure of 80 g in the inflamed paw was discarded. Drugs were dissolved in distilled water and administered subcutaneously. One hour after drug administration the animals were again screened and percent increase in pain threshold in each paw was determined.

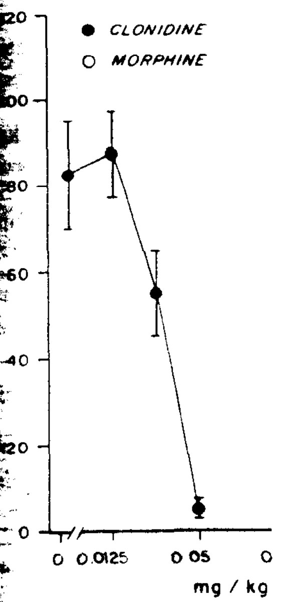
Morphine dependence and withdrawal. Male Long-Evans rats were implanted with indwelling jugular catheters as described by Numan *et al.* (19[illegible]). After surgery the rats were treated with an antibiotic for 1 day. The catheter was passed from the rat harness through a spring support to the top of the Plexiglas chamber where it was connected to a swivel and an injection system located outside the chamber *via* polyethylene tubing. The rats were continuously injected with morphine sulfate. A starting dose of [illegible] mg/kg/day was gradually increased to a maintenance dose of 99 mg/kg/day in 4 days. The maintenance dose was continued for at least 4 additional days before withdrawal. To precipitate withdrawal the infusion pumps were turned off and the rats were observed for withdrawal shakes beginning at 8 hr after discontinuation of the drug infusion. These procedures were recently described elsewhere (Hynes *et al.*, 1978).

For observation of "wet-dog" like body shakes associated with withdrawal, the chamber doors were opened and food cups removed. Each rat was observed for a period of 30 min during which the occurrence of withdrawal body shakes were counted. Body shakes were defined as violent shaking movements of the head and/or body of the rat which resemble the action of an animal that has been drenched with water (Gianutsos *et al.*, 1975). Clonidine was then injected [illegible] and 30 min after this treatment the rats were observed again for the occurrence of body shakes for another [illegible] min.

The effectiveness of the test drug was determined by comparing the withdrawal shakes observed on the same day before and after the drug treatment. Therefore, the predrug shakes served as a sign of withdrawal against which the effectiveness of the test drug was evaluated. This procedure of measuring withdrawal shakes and their alteration by drugs has recently been described (Lal and Hynes, 1977, 1978; Hynes *et al.*, 1978).

Results

As illustrated in figure 1, abdominal constriction induced by phenylquinone was blocked by both morphine and clonidine, each in a dose-dependent manner. Clonidine (ED50 = 0.03 mg/kg s.c.) was 17 times more potent than morphine (ED50 = 0.5 mg/kg s.c.). Morphine-induced inhibition of abdominal constriction was antagonized (71% antagonism) by naloxone, as expected. However the effectiveness of the anticonstriction action of clonidine was not antagonized by naloxone (table 1).



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hine	2.0	20 ᵃ	0.4 ±
dine	0.05	10	1.3 ±
one	1.0	20 ᵃ	33.3 ±
hine	2.0	10	
+			
loxone	1.0		26.5 ±
Clonidine	0.05	10	
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loxone	1.0		1.5 ±

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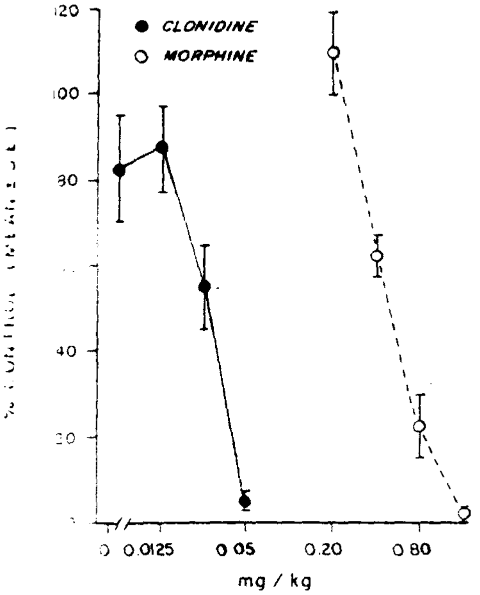

Fig. 1. A comparison of clonidine with morphine in blocking phenylquinone-induced abdominal constriction in mice. In saline-pretreated mice an injection of phenylquinone caused a mean of 41 (± S.E., 4.77) constrictions. Number of constrictions produced after test drug in each mouse was divided by the saline mean to obtain the data plotted on the Y-axis.

TABLE 1

Effect of morphine, clonidine and naloxone on phenylquinone abdominal constriction in mice

Drug	Dose	N	Mean Constrictions (± S.E.)	% Inhibition of Abdominal Constrictions
	mg/kg s.c.			
Vehicle		40 [a]	36.9 ± 1.9	
Morphine	2.0	20 [a]	0.4 ± 0.2	99*
Clonidine	0.05	10	1.3 ± 0.4	96*
Naloxone	1.0	20 [a]	33.3 ± 3.2	6
Morphine	2.0	10		
+				
Naloxone	1.0		26.5 ± 4.7	20
Clonidine	0.05	10		
+				
Naloxone	1.0		1.5 ± 1.5	96

[a] Data pooled from two tests. No significant variance according to F-maximum test for homogeneity of variances.

* $P < .001$ calculated by Student's T test compared to control values.

Clonidine and morphine also inhibited the tail-flick response in mice elicited by radiant heat, in a dose-dependent manner, with ED50 values of 0.7 and 3.8 mg/kg s.c., respectively (fig. 2). Again, whereas the action of morphine was antagonized (62% antagonism) by naloxone, no such antagonism of the action of clonidine was seen (table 2). Phenoxybenzamine, an *alpha* adrenergic blocking agent, also showed little effect in reversing tail-flick inhibition produced by clonidine (table 2).

Clonidine and morphine were also effective in blocking tail withdrawal from hot water in rats.

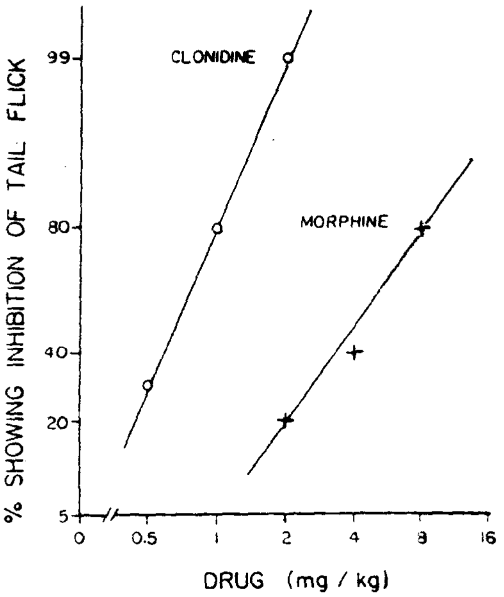

Fig. 2. A comparison of clonidine with morphine in blocking heat-induced tail-flick response in mice. Increase in latency greater than 2 S.D. was taken as a positive response of analgesia. Mean tail withdrawal latency of all mice before they were treated with a drug was 1.78 sec.

TABLE 2

Effect of morphine and clonidine on tail-flick response

Drug	Dose	N	% Inhibition of Tail Flick [a]
	mg/kg s.c.		
Vehicle		20	0
Morphine	8.0	20	80
Clonidine	1.0	20	80
Phenoxybenzamine	10.0	10	20
Naloxone	1.0	20	0
Morphine	8.0		
+			
Naloxone	1.0	20	30
Clonidine	1.0		
+			
Naloxone	1.0	20	80
Clonidine	1.0		
+			
Phenoxybenzamine	10.0	20	80

[a] Increase of response latency greater than 2 S.D.

In this test the effective dose of clonidine was in a range similar to that of morphine (table 3). Again, while the activity of morphine was antagonized by naloxone, the action of clonidine was not.

In the modified Randall-Selitto test, clonidine shows a significant inhibition of the pain response in both the inflamed and noninflamed paws (table 4). In comparison of the effect of clonidine and morphine on the inflamed paw it can be seen that clonidine (200% increase at 1 mg/kg s.c.) is approximately 4 times as potent as morphine (238% increase at 4 mg/kg s.c.) in preventing the pain response. The data collected from measurements on the noninflamed paw show clonidine to be effective in inhibiting the pain response. However, the effect was not very potent and was not dose-dependent. In this regard also clonidine data resembled those of morphine as reported by others (Randall and Selitto, 1957).

Data summarized in figure 3 show clonidine to be very effective in blocking "wet-dog" shakes induced by abstinence-precipitated withdrawal in morphine-dependent rats. The clonidine effect was dose-dependent ($r = 0.95$, $P < .01$) and an ED50 value of 0.02 mg/kg was obtained. Naloxone (5 mg/kg s.c.) failed to antagonize the effect of clonidine. Blockade of withdrawal shakes by morphine (ED50, 14 mg/kg) and its antagonism by naloxone has been reported previously (Lal and Hynes, 1978).

Discussion

Clonidine is a central noradrenergic agonist (Hoefke and Kobinger, 1966; Anden *et al.*, 1970) which is believed to act on presynaptic *alpha*

TABLE 3

Inhibition of tail withdrawal response induced by warm water treatment

Drug	Dose	*N*	% Showing Inhibition of Tail Withdrawal[a]
	mg/kg s.c.		
Saline		20	0
Naloxone	5	10	0
Clonidine	2.5	12	85
	10.0	12	75
Morphine	2.5	12	58
	5.0	12	75
	10.0	12	92
Naloxone	5		
+			
Morphine	10	10	0
Naloxone	5		
+			
Clonidine	2.5	6	75

[a] Percentage of animals showing tail withdrawal latency greater than sum of mean and 2 S.D. obtained in saline-treated rats.

TABLE 4

Effect of morphine and clonidine on Randall-Selitto pain response

Drug	Dose	Applied Pressure[a]		
		Predrug[b]	Postdrug	% change[c]
	mg/kg s.c.		g	
Morphine	0.0	67 ± 5	80 ± 12	19
Inflammed	0.5	78 ± 4	80 ± 10	3
Paw	1.0	77 ± 5	140 ± 30	82**
	2.0	77 ± 4	145 ± 33	88*
	4.0	77 ± 6	264 ± 52	238**
Clonidine	0.0	52 ± 4	46 ± 2	−12
Inflammed	0.125	48 ± 2	62 ± 6	29
Paw	0.25	46 ± 4	72 ± 6	[illegible]
	0.5	48 ± 4	84 ± 10	[illegible]
	1.0	50 ± 4	150 ± 10	200
Clonidine	0.0	74 ± 6	66 ± 4	−11
Non-Inflammed	0.125	48 ± 4	74 ± 10	54*
Paw	0.25	56 ± 8	62 ± 8	11
	0.5	58 ± 4	66 ± 8	14
	1.0	66 ± 8	98 ± 10	48*

* $P < .05$ calculated by paired *t* test compared to predrug values.

** $P < .01$ calculated by paired *t* test compared to predrug values.

[a] Data are mean ± S.E. grams of pressure applied to elicited pain response. Mean is based upon 10 rats in each group.

[b] All predrug controls were compared and no significant variance was shown according to *F*-maximum test for homogeneity of variances.

[c] Percent change from predrug controls.

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Discussion

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Applied Pressure*	
Postdrug	% chan
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80 ± 10	3
140 ± 30	82
145 ± 33	88
264 ± 52	238
46 ± 2	−12
62 ± 6	29
72 ± 6	56
84 ± 10	75
150 ± 10	200
66 ± 4	−1
74 ± 10	54
62 ± 8	10
66 ± 8	14
98 ± 10	48

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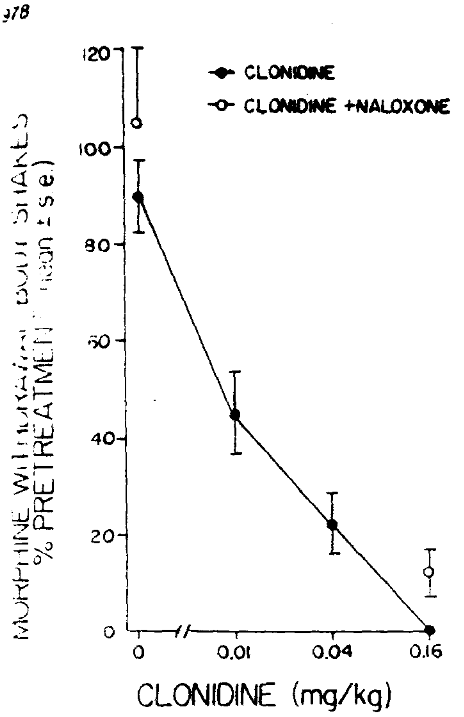

Fig. 3. Effect of clonidine given intraperitoneally on morphine withdrawal body shakes. Data are presented as a percentage of preclonidine shakes. Naloxone was given a dose of 5 mg/kg. Naloxone doses lower than this dose were also ineffective (data not included).

receptors at low doses (Anden *et al.*, 1970). Additionally, it has been proposed that clonidine stimulates central epinephrine receptors (Bolme *et al.*, 1974). A number of investigators have shown that clonidine inhibits activity in central serotonergic neurons (Anden *et al.*, 1070; Maj *et al.*, 1973; Svensson *et al.*, 1975) and that it inhibits the release of acetylcholine in an isolated guinea-pig ileum preparation (Deck *et al.*, 1971; [illegible]er *et al.*, 1972) as well as shows cholinomimetic properties on behavior and brain cyclic nucleotides (Gumulka *et al.*, 1977). Clonidine has also been shown to stimulate histamine H_1 receptors in the heart (Csongrady and Kobinger, 1974) and to activate central H_2 receptors in anesthetized rats (Karppanen *et al.*, 1976; Sastry and Phillis, 1977). Clinically, clonidine is employed in the control of hypertension. However, in recent years use of clonidine has been explored for many other conditions such as the treatment of alcohol withdrawal (Bjurkavist, 1975) and prevention of migraine headache (Brogden *et al.*, 1975).

Our approach in this comparison of clonidine and morphine was to use a series of most often used procedures to screen analgesic drugs in order to measure relative "analgesia" in laboratory animals. In all cases, clonidine has shown significant activity which was greater than or equal to that of morphine and unlike morphine, clonidine activity is not reversed by naloxone.

The mechanism of action of clonidine in producing analgesia is unclear. Increased turnovers of norepinephrine in the brain stem and dopamine in the telencephalon are reported to be of importance in analgesia (Paalzow, 1974). The activity of clonidine in stimulating central norepinephrine receptors can then be related to a stimulation in the lower brain structures (Paalzow, 1974). Presynaptic activation of *alpha* receptors by clonidine (Anden *et al.*, 1970) explains the inhibitory effect which clonidine has upon noradrenergic neurons (Starke, 1972; Svensson *et al.*, 1975) since we have shown that phenoxybenzamine, a postsynaptic *alpha* adrenoreceptor blocker failed to block the effect of clonidine in the tail-flick test. This confirms another report on clonidine-phenoxybenzamine interactions in which it was shown that phenoxybenzamine blocked certain aspects of the actions of clonidine and not others (Anden *et al.*, 1976). An alternate explanation has been proposed involving an activation of central epinephrine receptors which have been found on noradrenergic nerve cells in the locus coeruleus (Hokfelt *et al.*, 1973, 1974; Koslow and Schlumpf, 1974). This activation could decrease activity in the noradrenergic neurons (Fuxe *et al.*, 1974). The inhibitory action of clonidine on the serotonin system (Anden *et al.*, 1970; Maj *et al.*, 1973; Svensson *et al.*, 1975) may not play a rôle in its analgesic effect as it would be expected to decrease analgesia. The raphe nucleus is believed to play a role in pain perception and this structure is rich in serotonergic neurons. Serotonin is thought to decrease emotional reactivity to pain (Tenen, 1967). It is also apparent that the analgesic activity of clonidine is not mediated through a narcotic or endorphin mechanism. In all instances, naloxone failed to antagonize the action of clonidine.

Because clonidine is an antihypertensive, and in higher doses, a sedative drug, one must consider the possible role of the hypotensive effects and sedation in the apparent response in analgesia tests. Phenoxybenzamine is also an effective antihypertensive agent at the dose used in the tail-flick test but is devoid of analgesic activity. Similarly, other antihypertensive drugs such as reserpine and methyldihydroxyphenylalanine are not analgesics. Also, the doses found active in analgesia testing are not hypotensive in normotensive rats. Based upon these considerations we believe that the action of clonidine in causing analgesia is not directly related to its hypotensive effect. However, further research is needed to determine this conclusively. Antinociceptive doses of clonidine were sometimes similar to those usually reported to produce behavioral sedation. However, sedation *per se* is not likely to be the basis of analgesia. Sedative drugs such as barbiturates and benzodiazepines, and neuroleptics such as haloperidol that produce catalepsy, do not give analgesia-positive reactions in the laboratory tests described above. Further testing utilizing other pharmacological and physiological methods needs to be done in order to elucidate the mechanism of the analgesic action of clonidine.

Wet-dog shakes are considered to be reliable signs of narcotic withdrawal in the rat and in several other animal species (Gianutsos *et al.*, 1975; Lal and Hynes, 1978; Martin *et al.*, 1963). The data presented here show that clonidine is able to suppress the withdrawal body shakes in morphine-dependent rats to a degree comparable to that shown by morphine and methadone (Gianutsos *et al.*, 1975; Lal and Hynes, 1978) as well as haloperidol (Lal and Numan, 1976) and butaclamol (Hynes *et al.*, 1978). This action of clonidine is also found in naloxone-precipitated withdrawal in morphine-dependent rats (Tseng *et al.*, 1975).

Our data are relevant to a recent clinical observation that clonidine reversed the withdrawal syndrome after discontinuation of methadone administration in opiate-dependent patients (Gold *et al.*, 1978).

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